1. Plant Metabolism: The Big Picture

Metabolism is the integrated network of enzyme-mediated and carefully regulated chemical reactions that allows organisms to live, grow and reproduce.

- All organisms transform and interconvert many organic compounds.
- They require energy, mainly in the form of **ATP**.
- They require building blocks for construction of their own tissues.
- The pathways involved are called **metabolic pathways**; the overall network may be called **intermediary metabolism**.

Important molecules of life include **carbohydrates, proteins, fats and nucleic acids**.

Primary Metabolism in Plants

- Primary metabolism consists of fundamental reactions essential for plant life.
- Photosynthesis converts light energy into chemical energy and produces carbohydrates.
- Respiration degrades organic molecules and releases usable energy.
- Major primary products include carbohydrates, fats, proteins and nucleic acids.

Photosynthesis: $6CO_2 + 6H_2O + light \rightarrow C_6H_{12}O_6 + 6O_2$

Primary metabolites are broadly similar among organisms because the basic requirements for life are similar.

2. Primary vs Secondary Metabolites

Primary metabolites

- Produced through fundamental metabolic pathways.
- Essential for growth, development and reproduction.
- Examples: carbohydrates, fats, proteins and nucleic acids.

Secondary metabolites

- Not directly required for the essential metabolism and immediate growth of the cell.
- Usually low-molecular-weight compounds with more restricted distribution in nature.
- Their production may depend on species, developmental condition and environmental factors.
- They help adaptation and ecological interactions and can contribute to the organism's phenotype.
- They are derived from primary metabolites through specialized secondary metabolic pathways.
- Most pharmacologically active natural products are secondary metabolites.

Important functions of secondary compounds

- Ecological interactions between plants and other organisms.
- Pigments such as **anthocyanins** color flowers red/blue and attract pollinators and seed dispersers.
- **Nicotine** and other toxic compounds may protect plants from herbivores and microbes.
- Some compounds, such as rubber and THC, have no clearly established essential function in the plant in the context of the slides.

Key principle: Primary metabolism supplies energy and building blocks; secondary metabolism modifies these building blocks into specialized natural products.

3. Examples and Classification of Secondary Metabolites

Examples with medicinal importance

- **Digoxin** - cardiotonic; obtained from foxglove (Digitalis lanata).
- **Morphine** - pain killer analgesic from opium poppy (Papaver somniferum); historically important as an early isolated plant active ingredient.
- **Aspirin** - pain killer analgesic and anti-inflammatory drug historically linked to willow (Salix spp.).
- **Penicillin** - antibiotic from Penicillium spp.

Major classes

Secondary compounds can be grouped according to similar chemical structures, biosynthetic pathways, or the types of plants producing them. The major classes emphasized are:

- **Alkaloids**
- **Terpenoids**
- **Phenolics**

Glycosides

- Secondary compounds frequently occur in combination with one or more sugars; these combinations are called **glycosides**.
- **Glycone** = sugar part.
- **Aglycone** = non-sugar part.
- Common sugars include glucose, galactose and rhamnose.
- **Apiose** is a distinctive sugar associated with parsley and close relatives in the slide material.

Glycoside = glycone + aglycone, connected by a glycosidic linkage.

4. Central Primary Pathways Supplying Secondary Metabolism

Glycolysis

- The final product emphasized is **pyruvic acid (3C)**.
- Pyruvate can undergo oxidative decarboxylation to form **acetyl-CoA (2C)**.
- Acetyl-CoA is a major backbone/precursor for many primary and secondary metabolites.

Energy-producing degradation

- Carbohydrate degradation proceeds through **glycolysis** and the **Krebs/citric acid/TCA cycle**.
- Oxidation of fatty acids by **beta-oxidation** also provides energy and acetyl-CoA.

Formation of shikimic acid

- **Phosphoenolpyruvate (PEP)** is a glycolytic intermediate.
- **Erythrose-4-phosphate (E4P)** comes from the pentose phosphate pathway.

PEP + E4P -> Shikimic acid

Deoxyxylulose phosphate

Pyruvic acid + glyceraldehyde-3-phosphate -> deoxyxylulose phosphate.

These connections explain why secondary metabolism cannot be separated conceptually from primary metabolism: its precursors are generated by central metabolism.

5. Acetyl-CoA: A Major Metabolic Junction

Acetyl-CoA can enter several pathways:

- **TCA/Krebs cycle** -> non-aromatic plant acids such as citric, succinic and malic acids.
- **Fatty-acid synthesis** -> acetyl-CoA and malonyl-CoA participate in building fatty acids.
- **Mevalonate pathway** -> terpenoids and steroids.
- **Acetate-malonate pathway** -> polyketide/aromatic and other acetate-derived products.

Formation of acetyl-CoA

- From pyruvate by oxidative decarboxylation.
- From fatty acids by beta-oxidation.

Acetate-Malonate Pathway

- A C2 building unit is supplied by **acetyl-CoA**.
- C2 units can form long alkyl chains such as fatty acids.
- They can also contribute to aromatic systems such as phenolic/polyketide products.
- For many aromatic acetate-derived products, acetyl-CoA is first converted to the more reactive **malonyl-CoA**.

Two groups emphasized:

- **Non-aromatic derivatives**: polyacetylenes (polyynes).
- **Aromatic polyacetates**: polyketides.

Do not confuse: MALONATE -> fatty acids/polyketides; MEVALONATE -> isoprenoids/terpenes/steroids.

6. Acetate-Mevalonate Pathway and Isoprenoids

Mevalonic acid is formed from **three molecules of acetyl-CoA**. It contains six carbons, but only five are retained in the isoprene building unit because the carboxyl carbon is lost.

3 Acetyl-CoA -> Mevalonate (C6) -> loss of carboxyl carbon -> Isoprene unit (C5)

Major products of the acetate-mevalonate pathway

- Isoprenoid compounds.
- Terpenes/terpenoids.
- Steroids.
- Cardiac glycosides.
- Saponin glycosides.
- Vitamin D.

Terpene classification by C5 isoprene units

Class	Isoprene units	Typical carbon number
Monoterpene	2	C10
Sesquiterpene	3	C15
Diterpene	4	C20
Triterpene	6	C30
Tetraterpene	8	C40
Polyterpene	many	variable/large

A useful sequence to memorize: **Mono C10 - Sesqui C15 - Di C20 - Tri C30 - Tetra C40.**

7. Shikimic Acid Pathway

Shikimic acid is a major building block for aromatic and phenolic natural products.

PEP (from glycolysis) + E4P (from pentose phosphate pathway) -> Shikimic acid

Important products

- **Aromatic amino acids:** phenylalanine, tyrosine and tryptophan.
- Phenols and phenolic glycosides.
- Cinnamic acid derivatives.
- Phenylpropane/phenylpropanoid derivatives.
- Lignins and lignans.
- Several aromatic alkaloids and related natural products.

Aromatic amino acids

The three amino acids emphasized are:

- **Phenylalanine (Phe)**
- **Tyrosine (Tyr)**
- **Tryptophan (Trp)**

Mnemonic: **P-T-T** = Phenylalanine - Tyrosine - Tryptophan.

Phenylalanine and tyrosine are especially important sources of phenylpropanoid building units, while tryptophan supplies indole-containing units.

8. Carbon Building Units in Natural-Product Biosynthesis

C1 unit

- The C1 methyl unit is supplied from **L-methionine**.
- L-methionine is activated to **S-adenosylmethionine (SAM)**.
- SAM contains positively charged sulfur and is an effective biological methyl donor.
- Methyl transfer commonly occurs by an **SN2 nucleophilic substitution** mechanism.
- Hydroxyl groups can give **O-methylation**; amino groups can give **N-methylation**; carbon nucleophiles can give **C-alkylation**.
- Methylenedioxy group: O-CH2-O.

C2 unit

- Supplied by **acetyl-CoA**.
- Used in fatty-acid chains and acetate/malonate-derived aromatic systems.
- Malonyl-CoA is a more reactive form used for many incorporations.

C5 unit

- The branched-chain **isoprene C5** unit comes from mevalonate.
- Mevalonate is formed from three acetyl-CoA molecules; one carboxyl carbon is lost to produce the C5 unit.

High-yield chain: **Methionine -> SAM -> C1 methyl**; **Acetyl-CoA -> C2**; **Mevalonate -> C5 isoprene**.

9. Amino-Acid-Derived Building Units

C6C3 (phenylpropyl/phenylpropane unit)

- Derived from the carbon skeleton of **L-phenylalanine or L-tyrosine**.
- Formation requires loss of the amino group.
- The C3 side chain may be saturated, unsaturated or oxygenated.
- Loss of one or two side-chain carbons produces shortened **C6C2** or **C6C1** units.

C6C2N

- Derived from L-phenylalanine or L-tyrosine; **tyrosine is more common** in the slide description.
- The carboxyl carbon is removed (decarboxylation), leaving the nitrogen-containing C6C2N skeleton.

Indole-C2N

- Derived from **L-tryptophan**.
- Tryptophan is a shikimate-derived aromatic amino acid.
- Decarboxylation removes the carboxyl carbon and leaves an **indole-C2N** unit.

Key comparison

- **Phe/Tyr - loss of amino group -> C6C3**.
- **Phe/Tyr - loss of carboxyl carbon -> C6C2N**.
- **Trp - loss of carboxyl carbon -> Indole-C2N**.

10. Ornithine and Lysine: C4N and C5N Units

C4N unit

- Produced from the non-protein amino acid **L-ornithine**.
- Usually found as a heterocyclic **pyrrolidine** system.
- Ornithine supplies its **delta-amino nitrogen**, not its alpha-amino nitrogen.
- The carboxylic acid function and alpha-amino nitrogen are both lost.

Ornithine -> C4N -> Pyrrolidine

C5N unit

- Produced in essentially the same way as C4N but uses **L-lysine** as precursor.
- The resulting heterocyclic system is **piperidine**.

Lysine -> C5N -> Piperidine

Why this matters

Ornithine and lysine are important alkaloid precursors because they provide nitrogen-containing carbon skeletons that can be cyclized and further modified during alkaloid biosynthesis.

Fast distinction: **C4N = Ornithine = Pyrrolidine**; **C5N = Lysine = Piperidine**.

11. Major Biosynthetic Routes of Secondary Metabolism

The chapter emphasizes three principal pathways, with an additional amino-acid-derived category used in the lecture notes.

Pathway	Main precursor logic	Major products/classes
Acetate-Malonate	Acetyl-CoA -> Malonyl-CoA; C2 units	Fatty acids, polyketides, aromatic polyacetates,
Acetate-Mevalonate	3 Acetyl-CoA -> Mevalonate -> C5 isoprene	Terpenes/terpenoids, steroids, cardiac
Shikimic acid	PEP + E4P -> Shikimate	Aromatic amino acids, phenols, phenylpropanoids,
Amino acid pathway	Direct use/modification of amino-acid s[illegible]	[illegible], cyanogenic glycosides, glucosinolates

12. Flavonoids: A Mixed Biosynthetic Origin

Flavonoids are especially important because their skeleton demonstrates how two pathways can contribute to one natural product.

Basic flavonoid skeleton = C6-C3-C6 (15 carbons)

- The **C6C3** contribution comes from the **shikimic acid/phenylpropanoid pathway**.
- The additional **C6** contribution comes from the **acetate-malonate pathway**, effectively through three C2-derived units.

Correct: Flavonoids = acetate-malonate contribution + shikimate/phenylpropanoid contribution.

Incorrect: Flavonoids from mevalonic acid + shikimic acid.

Acetate-derived natural products

- Acetate is ultimately supplied from carbohydrate metabolism via pyruvic acid and acetyl-CoA.
- Two major routes originate from acetate: **acylpolymalonate/acetate-malonate** and **mevalonic acid**.
- Acylpolymalonate route -> fatty acids and polyketides.
- Mevalonic acid route -> terpenes and steroids.

13. Final High-Yield Review

Memorize these pathway equations and associations:

- **CO_2 + H_2O + light -> glucose + O_2** (photosynthesis concept).
- **Glucose -> glycolysis -> pyruvate -> acetyl-CoA**.
- **PEP + E4P -> shikimic acid**.
- **Pyruvate + glyceraldehyde-3-P -> deoxyxylulose phosphate**.
- **3 acetyl-CoA -> mevalonate -> C5 isoprene**.
- **Methionine -> SAM -> C1 methyl transfer**.
- **Acetyl-CoA -> C2**.
- **Phe/Tyr -> C6C3**; shortened forms -> C6C2 and C6C1.
- **Phe/Tyr -> C6C2N** after decarboxylation.
- **Trp -> Indole-C2N** after decarboxylation.
- **Ornithine -> C4N -> Pyrrolidine**.
- **Lysine -> C5N -> Piperidine**.
- **Flavonoids -> C6-C3-C6** from shikimate + acetate-malonate contributions.